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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,870	05/09/2007	Brian M. Gallagher Jr	9626-4	4403
20792 7590 04/27/2009 MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627				
EXAMINER CHANDRAKUMAR, NIZAL S				
ART UNIT 1625		PAPER NUMBER		
MAIL DATE 04/27/2009		DELIVERY MODE PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/572,870

Applicant(s)

GALLAGHER JR ET AL.

Examiner

NIZAL S. CHANDRAKUMAR

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-90 is/are pending in the application.
- 4a) Of the above claim(s) 4, 7-10, 14, 15, 21, 26, 33, 34, 48-81 and 84-90 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82 and 83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

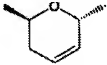
- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 03/21/2008
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____


DETAILED ACTION

Election/Restrictions

Applicants elect Group I in papers filed 02/17/2009. Applicants state that the election is with traverse only to the extent that claim 83 should be grouped with Group I. Applicants did not identify the claims encompassing the elected Group I.

In a telephone conversation with Robert Schwartzman, Examiner requested that applicant identify claims encompassing the elected Group I. Examiner also requested if applicant would redraw the claim structural formulae and amend claim language in accordance with the elected Group I in order to facilitate prosecution of the application, even though applicant is entitled to be his own lexicographer. Examiner made this request because in the claimed formula among other things, even the six atoms of the

ring in the structural moiety  is pictured with independently varying

eight variables as formula .

In subsequent papers filed 03/12/2009, applicant confirmed the election of Group I, identified 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82, and 83 as corresponding to elected group, requested inclusion of claim 83 with Group I; no amendments to claims were made.

As requested by the applicant, claim 83 is examined with claims of Group I. Because applicant did not distinctly and specifically point out the supposed errors in the

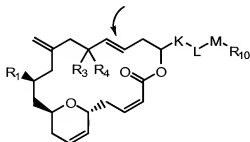
restriction requirement with respect to other Groupings, the election has been treated as an election **without** traverse (MPEP § 818.03(a)).

Claim 4, 7-10, 14, 15, 21, 26, 33, 34, 48-81, 84-90 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 02/17/2009.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Reiteration and structural definition of compounds of elected Group I (see election restriction papers filed 01/29/2009, last two lines of page 2 and first line of page 3:

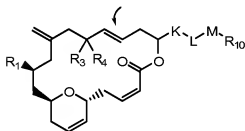
The formula of the elected Group I is



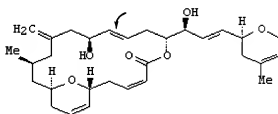
wherein the arrow indicates epoxide corresponding to the double bond, R1 is alkyl, K, L, M and R10 are as defined in the claims. Note that R1 alkyl is meant to correspond to the term 'aliphatic' of claim 1 and the definition as found in [0011] of the specification.

Although applicant withdrew many claims encompassing non-elected subject matter, the instant claims under prosecution still include large amount of non-elected subject matter. It is suggested that applicant amend the claims in accordance with the elected group I as shown above including stereochemistry and deleting non-elected subject matter. It is also suggested that applicant verify the correctness of structures S- Y on page 7 and 8 of claim 1. Further many claims indicated as encompassing elected group I depend on withdrawn claims. Appropriate corrections are expected.

Comparison of formula of elected group I and formulae of natural products laulimalide and desEpoxyaulimalide.



Instant claim formula



laulimalide and desEpoxyaulimalide

The differences between the two formulae are in the variables R₁, R₃, R₄, K, L, M and R₁₀/

The above comparison is made to clarify what is under prosecution and in view of *In re Zletz*, 13 USPQ2d 1320, 1322. “An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous.”

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term 'derivative(s)' render these claims indefinite as it implies more than what is being positively recited and therefore the structural make-up of the compounds embraced is unclear.

In claim 1, the variables R3 and R4 are defined in a way that would accommodate simultaneous presence of substituents such as OH or NH2 on the same carbon. One of skill in the art would anticipate such pattern of substituents to be impossible in the instant case. As such if a substituent is impossible, the claim can properly be rejected under 35 U.S.C. 112 paragraphs 1 or 2. A compound with an impossible substituent clearly cannot be made, and hence a paragraph 1 rejection is proper. Alternatively, if it is impossible, then it is not correct.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and dependent claims rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compounds of the formula, does not reasonably provide enablement for making prodrugs of compounds of the formula. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

There is insufficient disclosure with regards to 'prodrugs'. Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still

an experimental science. It is well known in the art that for a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large degree of experimentation. The disclosure relating to these tests is lacking in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

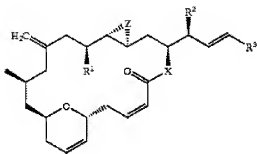
The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

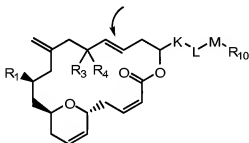
Claims 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82, and 83 rejected under 35 U.S.C. 103(a) as being unpatentable over Ashley et al. US 6670389.

Ashley et al teach Lulimalide analogs (see column 4 and 5)



corresponding to compounds of the
elect group I of the instant case.

The instant claims are drawn to Lulimalide analogs



The variables R1, R3, R4, K, L, M and R10
are commonly used substituents in the medicinal chemistry art. The K, L, M and R10
variables correspond to side chain of Lulimalide.

The difference are:

R1 of the instant case Vs methyl group of Ashley. However, note that in applicants
disclosed compounds R1 is methyl.

R1/R2 of the instant case Vs R1, R2 = 1-10C alkoxy, aryloxy or alkylaryloxy of Ashley.

Note Ashley groups are included in applicants of R1/R2; also note applicant has

included impossible substituents as possibilities for R1/R2 See rejections under 35 U.S.C. 112-2.

K, L, M and R10 of the instant case Vs R1 R3 containing chain of Ashley. However, note that Ashley R1 and R3 fall within the description of K, L, M and R10 of the instant case.

Ashley does not teach all the conceivable compounds encompassed by the elected Group I. However, it is to be noted that instant claim while encompassing generically claimed compounds of Ashley, excludes compounds exemplified by Ashley to negate possible anticipatory rejection.

Resolving the level of ordinary skill in the pertinent art:

It would have been obvious to one of ordinary skill in the art to make further compounds similar to the compounds of Ashley with the reasonable expectation of success because Ashley teaches that the substitution groups of Laulimalide corresponding to K,L,M and R10 are not deleterious to the Laulimalide like activity but provide opportunity for medicinal chemistry optimization of properties using commonly employed substituents. Major portion of the instantly claimed compounds and Laulimalide derivatives of Ashley are the same. Obviousness based on similarity of structure and functions entails motivation to make the claimed compounds in expectation that compounds of similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

Likewise,

Claims 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82, and 83 rejected under 35 U.S.C. 103(a) as being unpatentable over Ghosh US 7109235 and WO 03/076445.

Ghosh teaches Laulimalide derivatives similar to the compounds of the instant case. The differences are mainly in the K,L,M and R10 containing side-chain substituents. Ghosh teaches many modifications including heterocyclic (similar to compounds of instant claim 44) modification of Laulimalide side chain. Instant claims exclude compounds of Ghosh et al. by proviso. The major part of (laulimalide structural template) of the instant claims and that of Ghosh are the same. The differences are commonly used substituents in the medicinal chemistry art, modifications routinely used for optimization of properties. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

Likewise,

Claims 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82, and 83 rejected under 35 U.S.C. 103(a) as being unpatentable over Mooberry US 6414015 6670389 7109235.

As explained above, Mooberry teaches Laulimalide derivatives similar to the compounds of the instant case. The differences are mainly in the K,L,M and R10 containing side-chain substituents. Instant claims exclude compounds of Mooberry by

proviso. The major part of (laulimalide structural template) of the instant claims and that of Mooberry are the same. The differences are commonly used substituents in the medicinal chemistry art, modifications routinely used for optimization of properties. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5, 6, 11-13, 16-20, 22-25, 27-32, 35-47, 82, and 83 rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Ashley et al. US 6670389 and Ghosh US 7109235.

The difference between the compounds of the instant claims and the compounds of the prior art are the substitution pattern on the periphery of laulimalide ring system, particularly in the side chain (variables K, L, M and R10). These differences are interchangeably and commonly used substituents in the medicinal chemistry art. For example Ashley et al teach modification of laulimalide side chain by deletion of hydroxy group or by acylation of this hydroxyl group or etherification of this hydroxyl all resulting in compounds encompassed by the instant claims. Likewise, Ghosh teach heterocyclic modification of laulimalide side chain. Based on such prior art teachings, namely that a wide variety of side chain modifications (corresponding to instant K, L, M and R10) is well tolerated for retention of laulimalide-like pharmacological property, it would have been obvious to one skilled in the art at the time of the instant application that to make additional analogs for routine optimization of properties using commonly employed substituents. The instantly claimed compounds would have been suggested and thus obvious to one skilled in the art. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds of similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nizal S Chandrakumar/
Examiner, Art Unit 1625

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625